Tools for better health care

Radiation sterilization of medical supplies is set for rapid growth

by Ramendra Mukherjee

In the history of medical care, the development and use of the "concept of asepsis" can be credited as a major breakthrough in achieving successes of clinical practice. Despite superior surgical skills, a clinical operation could "fail" even if one item used in surgical intervention remained "unclean" — that is, if it were associated with some contamination of microbes.

Investigations on the "etiology", or causative factors, of infective diseases have long established that one major route is through "cross-transfer" of pathogens from an infected patient to another patient and/or an otherwise healthy person. This type of cross-infection — also known as "nosocomial disease" — accounts for a large proportion of all cases of ill health, morbidity, and mortality suffered by mankind. In view of deficient standards of health care and hygiene, the prevalence and risks of such health hazards could be even greater in developing countries.

The gravity of the situation has been illustrated dramatically. One report, by the World Health Organization (WHO), cites a catastrophic outbreak of infective ebola fever at Yambuki in Zaire killing more than 280 people within a few days. It was discovered that in the hospital concerned, only five syringes and hypodermic needles were used each day to treat all ward patients and an additional 400 out-patients. A pan of water was usually used to rinse the needles, which were only occasionally boiled for better decontamination. The report

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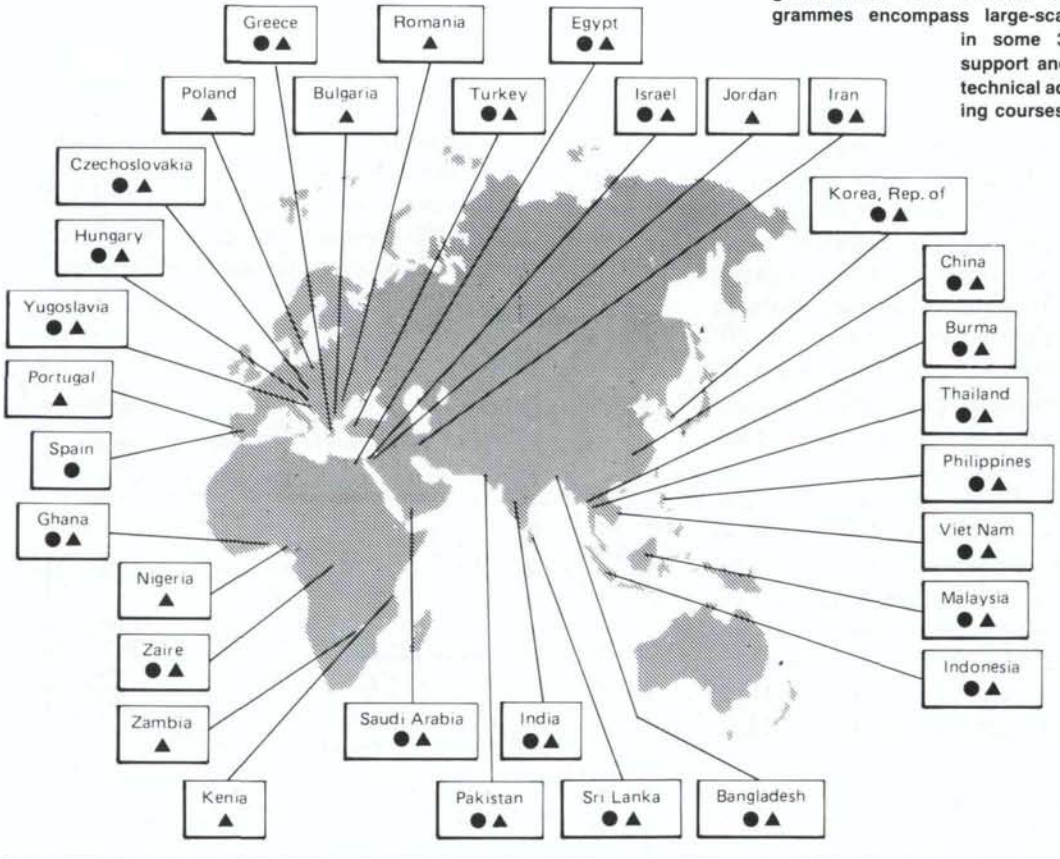
Radiation-sterilized medical supplies have made inroads into the health care systems of many developing countries, largely through promotional programmes over the past 10 years sponsored by the IAEA, the United Nations Development Programme, and regional intergovernmental and national organizations. The programmes encompass large-scale irradiation facilities in some 30 countries, research support and co-ordinated projects, technical advisory assistance, training courses and fellowships.



further noted that the epidemic vanished as dramatically as it appeared as soon as this unhygienic practice of medical injections ceased.*

Such reports suggest that continuing risks could threaten the health and welfare of people in countries through an unlimited spectrum of serious diseases, including even AIDS (autoimmune deficiency syndrome), debilitating hepatitis, and many others via contaminated hypodermics and other unsatisfactory medical devices used in the health care system.

They also underscore the fact that the health care system could end up in "failure" and be "self-defeating" if the crucial area of providing "sterile" medical supplies — those free from any association of microbial contaminants — remains neglected. The process of rendering a medical item sterile through "complete" destruction and/or removal of such contaminants to enhance clinical safety is known as *sterilization*.

Methods and practices

The principle behind the sterilization process is based upon the suitable application of a physical, chemical, and/or mechanical agent or agents to destroy, kill, or remove contaminants, without "adversely damaging" the medical item concerned — that is, without rendering it unfit for the desired safe clinical use. Among methods that have been conventionally used are: wet and dry heat; chemicals with defined biocide activity, such as toxic ethylene oxide gas (ETO); formaldehyde; and filtration.

Since the 1950s, the applicability of ionizing radiation for medical product sterilization has been recognized, as part of comprehensive industrial manufacturing processes. In these industrial applications, radiation processing techniques have held an important edge over conventional counterparts — namely, heat and ETO. Advantages particularly relate to the ability to penetrate materials, even after final packaging, and none or negligible rises in temperature during treatment, which permits processing of heat-sensitive plastic polymer materials. Other significant attributes compared to alternatives are energy economy and conservation, as well as preservation of environmental quality through a pollution-free operation of the technology and, presumably, a superior sterility assurance of the finished product.

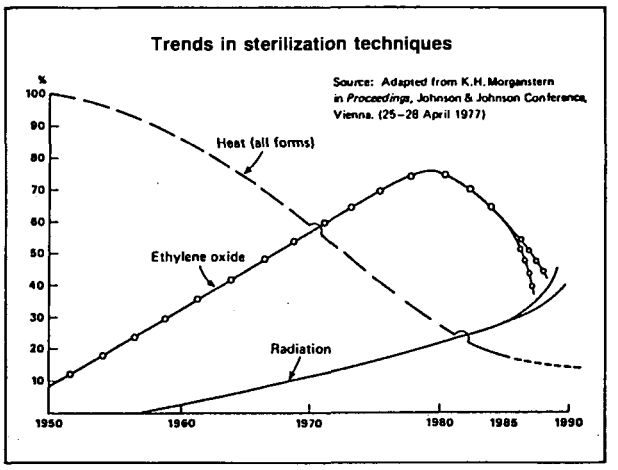
One further advantage of radiation — possibly of special significance in the context of technology transfer to developing States — is the high ease and reliability in the control of the technology. Unlike both heat and ETO sterilization processes, which require an "integrated control" of temperature, humidity, vacuum, pressure, time, concentration, wrapping, and other factors, the successful operation of the radiation sterilization process requires only control of "exposure time" estimated to deliver the correct radiation dose by a pre-calibrated irradiator. This feature, therefore, proves to be especially advantageous in terms of "low technology" since the process exacts relatively lower demands for high-level skilled operation and maintenance.

Status and trends

Before the 1950s, health care systems in developed and developing countries alike relied almost exclusively upon "re-usable" medical supplies. The principal technique of sterilization for those heat-resistent items involved moist heat (i.e. autoclaving) or dry heat (i.e. processing in ovens). Industrial innovation in technologically advanced countries of Europe and North America during the mid-1950s and primarily the 1960s was spurred by a new class of polymer materials. Besides being economical, they exhibited enough attractive physical and chemical properties to serve as possible constituents of a growing range of "single-use" medical products and their protective sealed packages.

However, most of these polymers could not tolerate high temperatures of traditional thermal sterilization processes, and there was a growing need for a process that could work at near room temperatures: in other words, "cold sterilization".

The availability of large cobalt-60 radioisotope sources, which emit high-energy, deep-penetrating gamma radiation, provided an alternative solution for sterilizing these new class of medical supplies. Another type of radiation, based upon electrical machine-generated electron beams also was useful. (As part of technology-transfer activities to developing Member States, technical criteria and guidelines for the choice of different plastic formulations suited to radiation processing should be provided.) Additionally, ETO was in use as a "cold sterilization" process, and it still caters for a major share of the demand, despite a progressive decline for reasons associated with health and environmental hazards.



* See *Bulletin of World Health Organization*, No. 56 (1978). Other incidents have been reported on the outcome of a WHO survey on nosocomial infection in Central Africa.

Currently, ETO seems to have gone past the "hump" and is on a sharp decline, particularly in North America and Europe. (See accompanying chart.) In contrast, radiation technology is steadily rising. It appears that ETO's decline would continue to be balanced to a large extent by growth of radiation sterilization, if problems of cobalt-60 supply do not become a limiting factor. Obviously, there are big unknowns involved in the field, and the relative proportions suggested in the chart should be construed as tentative.

Rapid move to radiation

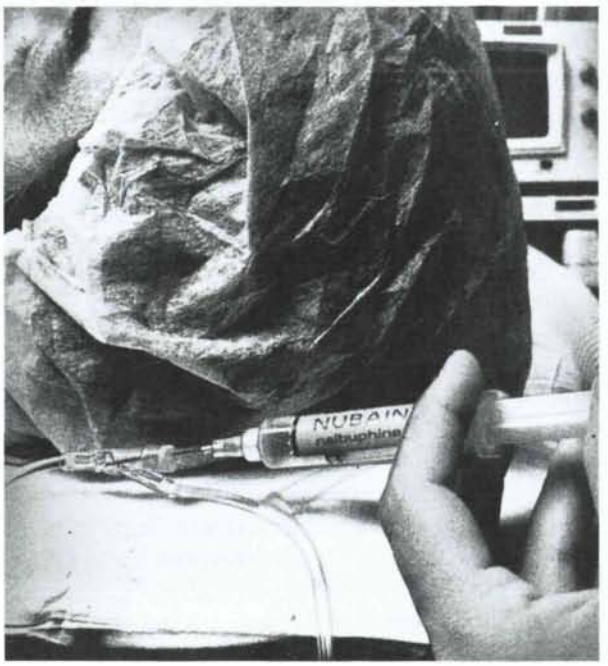
During the past 15 years, radiation processing as a whole is estimated to have grown steadily at about a 10 to 15% rate per year. One reliable indicator may be data on the number and total installed capacity of radiation sources.

Currently, more than 130 industrial gamma irradiators using cobalt-60 are installed in 42 countries, representing a processing capacity of approximately 200 million cubic feet of medical devices annually. In North America alone there are 53 irradiators with a combined design capacity of 100 million curies capable of processing 70 to 90 million cubic feet of medical products annually. (In the United States, contract sterilization of disposable medical supplies alone accounted for $26 million in revenues in 1985, according to the Atomic Industrial Forum.) This represents a rapid increase in the use of gamma sterilization from an estimated modest 10% of all medical device sterilization in 1977, when the major share of sterilization was attributable to ETO, to as much as 40% in 1985. By 1990, gamma sterilization is expected to account for about 80% of all disposable medical product sterilization in North America.

Worldwide geographic distribution, with particular regard to regions relatively new to this technology, reveals a number of interesting facts. During the past decade (1975-85) there has been a significant rise in developing regions of Asia, Africa, and Latin America in installed gamma capacity engaged in sterilization processes. Collectively, this accounts for as much as 20% of the current world total.

Despite the recent spurt in North America, the situation in Europe, when it comes to gamma sterilization, is still somewhat ahead in net quantitative terms. The situation, however, is reversed for electron beam sources. The major share of electron beam use is in North America.

Japan has continued to place an emphasis on applications of accelerators for medical supply sterilization on the premise that electrons cause less physical/mechanical degradation and the delivery of a high-dose rate seems to prevent oxidative deterioration of products, which could also be significant for pharmaceutical substances, among others. All these observations suggest a continued bright future role for radiation applications in sterilization of medical supplies.



Sterilized needles and syringes are essential to safe medical care. (Credit: E.I. du Pont de Nemours & Co.)

Technology transfer

The irradiator type, size, and design, plus the operational policy of the irradiation facility and requirements for various categories of trained technical and maintenance personnel infrastructures, are generally dictated by several factors: (1) types of medical supplies used in public health services and by the medical profession; (2) the current and projected average annual demand for different medical products; (3) status of local manufacturing capability and the attitude of local manufacturers of medical products towards adoption of the radiation sterilization technique; (4) legal and public health clearance aspects of radiation-sterilized products; and (5) the cost of the final sterile products. Although the detailed situation may vary from one country to the other, the following "source" parameter considerations may hold a general relevance:

- In industrial and pilot-scale operations for radiation sterilization of medical products, gamma rays from cobalt-60 have been most frequently utilized worldwide (four times or more of installed capacity as compared to accelerators), and exclusively so in the Agency's developing Member States. For conditions in many developing countries, experts associated with relevant IAEA technical co-operation projects have generally recommended cobalt-60 gamma sources in either dry or wet storage systems.
- Experiences in many countries indicate that dependence on the large-scale availability of skilled engineers and technicians is less for radioisotope sources than for electron accelerators in the course of routine operation, maintenance, and servicing. Furthermore, one must consider the fact that irradiation facilities in developing

States most likely have to be designed for "service sterilization" to a number of different manufacturers of medical supplies. This seems to imply that the source must be geared to deal with a number of different product specifications. Under such circumstances, the source geometry should allow a greater flexibility in accommodating different volumes, shapes, and sizes of the carton/box containers of pre-packed medical items and the conveyor should include a provision for variation of its speed. The source efficiency in the delivery of the prescribed minimum sterilizing dose should be evaluated during the commissioning protocol and monitored at routine operations through appropriate use of defined physical chemical dosimeters.

- Often, developing countries seem to prefer a "multipurpose" irradiator plant to be able to deal with medical devices, food, and other relevant items. In the context of introducing a broad-scope radiation processing technology under national policy planning, a concurrent emphasis needs to be assigned to all relevant branches of industrial advancement. Such an irradiator should preferably accompany a flexible conveyor feature, including "output" to lead finished sterile items to an isolated storage area to help avoid accidental mixture with pre-sterilized items and consequent risks of health hazards. Such multipurpose irradiator plants already are in use or being planned in more than a dozen countries, including Bangladesh, Belgium, Brazil, Egypt, Hungary, India, Indonesia, and Israel.
- Generally in developing countries, steps recommended for radiation health safety related to source operation, as well as environmental protection, need to be adopted, taking local conditions into account. For instance, automated interlocking devices, and the provision to shut down the source in the event of malfunction, should be installed. Irradiated "sterile" product boxes should clearly display appropriate labels with a distinctive colour change indicator for easy identification and process control.

In the case of toxic gases, their use, such as ETO in industrial sterilization, currently is being subjected to more and more rigorous quality control, particularly in technologically advanced States with established criteria for environmental health protection. This regulatory control was imposed following discovery in the 1970s of potent mutagenic and carcinogenic effects of ETO residues on processed medical supplies and also in working environments. In countries with restrictions on ETO application, there are defined levels of permissible ETO residues on medical supplies. Such low levels (e.g., as low as 1 ppm in the USA, Japan, and USSR) are difficult to attain with existing technology without provision of some expensive control devices. Consequently, manufacturers are progressively shifting over to the radiation sterilization technology.

This subject was reviewed in a recent executive advisory meeting of a United Nations Development Programme (UNDP) and IAEA co-operative project for Asia and the Pacific on radiation technology. Expressing concern, experts concluded that most developing Member States of IAEA do not have a "defined regulatory position" on ETO residue levels in their environmental and occupational health protection guidelines. This factor seems to have been instrumental in the choice of ETO technology in some recent instances by a number of developing Member States.

Volume of products sterilized

Over the last three decades, the variety of radiation sterilized medical supplies has increased so enormously that it is almost impossible to present anything that could claim to be a complete list. To name a few, the assortment includes bulk hypodermic syringes and needles; transfusion and infusion sets; absorbent and non-absorbent cotton; surgical gloves; medical devices and instruments; cotton gauze and dressings; surgical blades; surgical dressings; lancets; pharmaceutical containers; specified medicaments; cat-gut and silk sutures; maternity kits; vasectomy kits; intra-uterine devices; scafold and other temporary implants as surgical aids; permanent inorganic implants; food for pathogen-free diets for immune-compromised intensive-care patients; biological and prophylactic preparations, and a wide range of non-viable biological tissue grafts.

The broad applicability of radiation in a "cold sterilization process" has in turn stimulated innovation of a wide range of new manufacturing industries for medical disposables and their packaging. Additionally, biological tissue grafts, in growing demand for sterile clinical use in reconstructive surgery and in congenital and disease-associated deformities, rapidly are moving to become a suitable candidate for sterilization by ionizing radiation.*

Detailed data on production costs of sterile medical items are not easily available from all Member States. However, from provisional figures in a report at the recent UNDP/IAEA executive advisory meeting, the total annual cost of radiation-sterilized medical materials at India's cobalt-60 facility, ISOMED, was estimated to be about US $10 million, based upon 1984 production. In the context of India's total market for health care supplies, this volume is estimated to account for only 10%. Future growth is expected, as there are some specialized sectors of hospitals and industry where such sterile products are in growing demand. Comparable situations are anticipated in Egypt, Hungary, the Republic of Korea, and Yugoslavia, where Agency-supported programmes have helped implement radiation processing for local production of sterile medical supplies.

Worldwide, according to an IAEA estimate, the total value of irradiated medical products is more than US $2 billion, with steadily increasing trends in both quantity and quality.

* See "Atoms for health: A need in Asia", by R. Mukherjee, *IAEA Bulletin*, Vol.26, No.3 (September 1984).

Good manufacturing practices

Production of medical devices and supplies intended for sterile clinical use starts in the manufacturing factory, using raw materials and components, and ends in the sterilization procedure. Obviously, without adequate control of the production cycle and facilities, the last sterilization step alone cannot guarantee the desired sterility.

Operators of a successful plant must acquire site-specific knowledge regarding what potential contribution raw materials, equipment, the facility environment, and people may make to the "microbial load" of pre-sterilized products. While all these are important, people, or more specifically workers, could probably be the greatest contributors to product contamination.

In developing States, socio-economic conditions may tend to dictate a larger proportion of "manual" over "automated" operations — a factor that may hold a special significance for those regions when it comes to safety controls of sterile medical items. This is supported in numerous studies where specific plastic items, operated by automatic assembly lines, are among the least contaminated ones, when compared to items assembled manually. Plant hygiene for both people and the facility are thus essential ingredients for safe products in modern manufacturing operations, and the recommended protocol should constitute a "good manufacturing practice", or GMP, which serves one of the most important regulatory roles in quality control of products.

Hygienic standards

Over the past 50 years, the evolution of the concept of sterility control reveals at least three distinct periods of development, which may be defined as (1) the period of "innocence"; (2) the period of "doubt"; and (3) the period of "enlightenment".

Early regulatory microbiologists, in the period of "innocence", held the assumption that sterility is "absolute" and "sterility testing" of final products should give the "ultimate proof of sterility". With the progressive development of the faculty of statistics and of the probability theory, statisticians, however, disturbed microbiologists by establishing the concept that "sterility is a probability function" and not an absolute. In this view, sterility testing of products became almost "meaningless" because of the implied meagre probability of discovering instances of low levels of contamination (and hence the status of assurance becoming "doubtful"). Subsequent recognition, however, that a thorough technical knowledge of the sterilization process *per se*, and its control capability, should lay the basis and provide the greatest assurance of sterility initiated some major changes in operational criteria and philosophy. This is still evolving in light of new data and experiences from the technology, thereby placing us in a period of "enlightenment" heralded since the late 1950s.

Irradiation facilities for medical and other products are operating in more than 40 countries. (Credit: Isomedix)

Today, the simplicity and reliability of sterilization process control to promote a higher probability of product sterility is easily achievable with radiation. It requires only control of exposure time, while the alternative ETO treatment requires control of many factors.

The probability for safety assurance is generally numerically expressed as less than 10^{-6} and it has been given two interpretations:

- Less than one chance in one million that a contaminant will survive on a medical product
- Not more than one living microorganism in one million items.

The attempt is to express a theoretical concept in practical understandable terms. Nevertheless, what remains missing in health safety terms is the "estimation of the probability of an overt infection" being caused by "one such surviving organism" in a million processed medical items or by "one non-sterile item" among the group of a million items. This probability, although more difficult to define, is expected to be far less compared to the probability that a sterilization process would yield a non-sterile item.

Regulatory control aspects

Like all other sterilization processes, radiation sterilization, as well as the sterilized medical products for clinical use, must fulfil "validation criteria" as stipulated and implemented by the respective national food and drug administration, national pharmacopoeia commission, and other relevant health regulatory authorities. The purpose is imposition of the strictest quality control for radiation-processed items to ensure fulfilment of objectives for consumer safety. Often, radiation-processed items may have to be used beyond national boundaries. They must then comply as well with regulatory requirements of the consuming country. This is facilitated by criteria of international standardization,

which are distributed to co-ordinate and help implement suitable regulatory guidelines.

Countries pioneering in these efforts, such as Australia, the United Kingdom, and the United States have formulated guidelines to good manufacturing practices (GMPs) for sterile medical devices and surgical products, as well as for pharmaceutical products. Since the inception of radiation sterilization for medical supplies, the sterilizing dose of 25 kilogray generally has been followed in most countries.

Some distinctive specifications are now in practice, however. In North America, there happens to be no specified fixed minimum sterilizing radiation dose, and guidelines formulated by the Association for the Advancement of Medical Instrumentation (AAMI) are progressively implemented. These refer to dose-setting approaches based upon the estimated radiation resistance characteristics of naturally occurring microbial bioburden on medical products. Different sterility safety levels are thus achievable for different categories of medical items according to their clinical end uses. Consequently, many devices could in practice be radiation-sterilized at doses lower than 25 kilogray, while still others may justify an even higher dose. In contrast, European health regulatory authorities continue to follow and recommend a minimum sterilizing radiation dose of 25 kilogray.

This situation is expected to lead to some problems of international clearance of sterilized medical items and in attainment of implied health welfare objectives. Further joint analysis and review of problems and required technical steps should be facilitated through international standardization approaches.

In 1967, an IAEA expert group recommended the basis for an international code of practice for radiation sterilization of medical products. In co-operation with the WHO and national health regulatory authorities in Member States, the Agency remains responsive to periodic updating and revision of those recommendations in light of operational experiences in the field. One such review is planned during an IAEA advisory group meeting scheduled in Sri Lanka late in 1986. It is anticipated that these discussions will involve relevant expertise from health regulatory authorities, medical professionals, biomedical researchers, and manufacturers of sterile medical supplies.